Highly Enantioselective Synthesis of No-Carrier-Added 6-[^{18}F]Fluoro-L-dopa by Chiral Phase-Transfer Alkylation

Christian Lemaire,*[a] Steve Gillet,[a] Stéphane Guillouet,[b] Alain Plenevaux,[a] Joël Aerts,[a] and André Luxen[a]

Keywords: Amino acids / Enantioselectivity / Fluorides / Radiochemistry / Radiopharmaceuticals / Phase-transfer catalysis

[^{18}F]Fluoro-L-dopa, an important radiopharmaceutical for positron emission tomography (PET), has been synthesized using a phase-transfer alkylation reaction. A chiral quaternary ammonium salt derived from a Cinchona alkaloid served as phase-transfer catalyst for the enantioselective alkylation of a glycine derivative. The active methylene group of this Schiff-base substrate was deprotonated with cesium hydroxide and rapidly alkylated by the 2-[^{18}F]fluoro-4,5-dimethoxybenzyl halide (X = Br, I). The reaction proceeded with high yield (> 90%) at 0 °C or room temperature in various solvents such as toluene or dichloromethane. Preparation of the [^{18}F]alkylating agent on a solid support was developed. After labelling, the labeled [^{18}F]fluoroveratraldehyde was trapped on a ^{t}C18 cartridge and then converted on the cartridge into the corresponding benzyl halide derivatives by addition of aqueous sodium borohydride and gaseous hydrobromic or -iodic acid. Hydrolysis and purification by preparative HPLC made 6-[^{18}F]fluoro-L-dopa ready for human injection in a 25–30% decay-corrected radiochemical yield in a synthesis time of 100 min. The product was found to be chemically, radiochemically and enantiomerically pure (*ee* > 95%).

Introduction

Positron emission tomography (PET) is a molecular imaging technology that uses radiopharmaceuticals labeled with positron-emitting radioisotopes.[1] Among these radiopharmaceuticals, 6-[^{18}F]fluoro-L-dopa labeled with fluorine-18 (half-life 109 min), has found wide application as a tracer for in vivo cerebral studies of presynaptic dopaminergic functions in humans.[2] The need for reliable production of this radiopharmaceutical has led, in the last two decades, to reports on various electrophilic and nucleophilic radiosyntheses of this compound.[3,4] Routine productions of 6-[^{18}F]fluoro-L-dopa have been conducted in our laboratory for some time, using a nucleophilic, multistep radiosynthesis approach.[5] This method is based on the enantioselective alkylation of a chiral auxiliary previously described by Seebach et al. for the synthesis of amino acids.[6] This no-carrier-added (nca) regioselective and enantioselective approach involves a sequence with sensitive reagents. Consequently, the alkylation reaction, which requires the use of strong bases such as lithium diisopropylamide under anhydrous conditions, can be difficult to handle under remote control or to automate in the scope of routine production. This is undoubtedly the main limitation of this technique, which nevertheless permits large-scale production [> 100 mCi EOS (end of synthesis)] of 6-[^{18}F]-fluoro-L-dopa ready for PET injection with excellent chemical, radiochemical and enantiomeric purities (> 97%).

Numerous applications of phase-transfer catalysis (PTC) for the enantioselective syntheses (92% < *ee* < 99.5%) of a wide range of α-amino acids have been reported in the literature in the last few years.[7] These results prompted us to evaluate the potential of this attractive synthetic approach for the preparation of nca 6-[^{18}F]fluoro-L-dopa. This paper reports our first results with the PTC approach, which should overcome the main drawbacks of chiral auxiliary strategies.

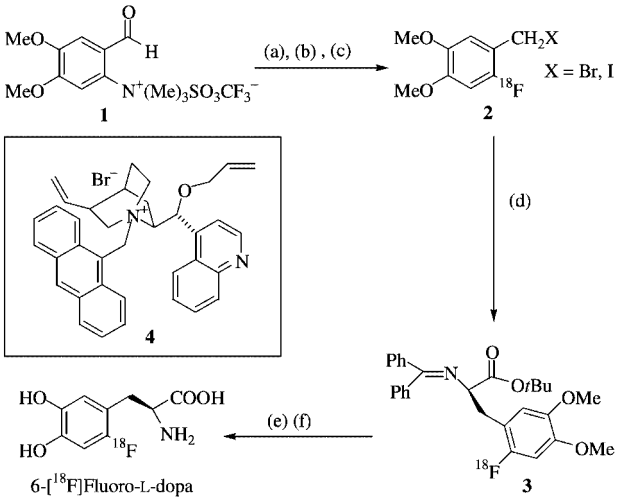
Results and Discussion

In the early 1990s, the first amino acid synthesis involving an asymmetric PTC appeared in the literature, although the reported enantiomeric excesses were quite moderate.[8] In 1997, the Corey and Lygo groups independently described very efficient PTC catalysts for amino acid synthesis.[9−11] More recently, several new chiral phase-transfer catalysts have also been presented in the literature.[7] Most of these, affording high enantiomeric excesses (> 90%), are generally derived from the quaternary ammonium salt of a cinchona alkaloid derivative. Among the described catalysts, those bearing an anthracenylmethyl substituent on the bridge-

[a] B-30 Cyclotron Research Center,
Liege University, 4000 Belgium
Fax: (internat.) + 32-43662946
E-mail: Christian.Lemaire@ulg.ac.be
[b] CERMEP,
59 Bd Pinel, 69003 Lyon, France

head nitrogen atom allow high catalytic enantioselective alkylations of *N*-(diphenylmethylene)glycine *tert*-butyl ester. Another important feature of this methodology is that almost equal and opposite enantiomers can be induced by switching from cinchonidinium to cinchoninium salts.[11] In light of this data from the literature, Corey's catalyst was selected for the nca synthesis of 6-[^{18}F]fluoro-L-dopa.[10]

The general synthetic pathway of this new radiochemical PTC approach involves three major steps (Scheme 1).

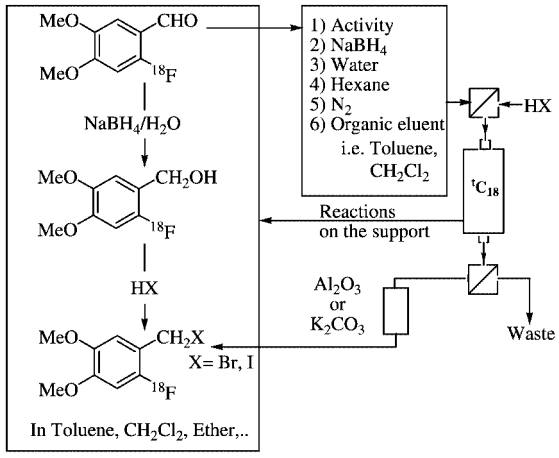


Scheme 1. Synthesis of nca 6-[^{18}F]fluoro-L-dopa by phase-transfer reaction; reagents and conditions: (a) [K/222] + $^{18}F^-$, DMSO, 110 °C, 45−50% EOB; (b) $NaBH_4$ aq., room temp., 100%; (c) HX(g), room temp., > 90%; (d) **4**, $(Ph)_2CNCH_2COOtBu$ (**5**), $CsOH·H_2O$, toluene, 0 °C, > 90%; (e) HI 57%, 200 °C, 20 min; (f) HPLC

The first step implies the preparation of an [^{18}F]fluorobenzyl halide (**2**) derivative. The second step consists of the alkylation reaction with a chiral catalyst (**4**) of a commercially available benzophenone imine, and the final step, the HPLC purification after hydrolysis.

Although numerous methods for the radiosynthesis of [^{18}F]fluorobenzyl halide have been reported,[12,13] in our opinion none of these methods is well suited for a simple automation and a reliable operation. Generally based on two or three reaction steps, they imply time-consuming operations such as evaporation, extraction, drying, and heating, making these syntheses inconvenient for routine use.

Reactions with reagents on a solid support have been rediscovered with the development of combinatory chemistry.[14] This solid-support approach, which has previously been applied with success in our laboratory to the alkaline synthesis of [^{18}F]FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose), should overcome these difficulties and avoid steps that are difficult to automate.[15] Thus, after labeling, the fluoroveratraldehyde derivative was trapped on a ^{t}C18 cartridge and quantitatively reduced on this same support with an aqueous solution of $NaBH_4$ (Scheme 2). The resulting [^{18}F]fluorobenzyl alcohol was then washed with water and dried on the solid support using a non-polar solvent.



Scheme 2. Radiochemical synthesis of the 2-[^{18}F]fluoro-4,5-benzyl halide alkylating agent on a ^{t}C18 Sep Pak cartridge

In order to be able to perform the halogenation with high yield (> 90%), the solid support has to be kept "wet" with hexane. The aryl iodide was then synthesized by passing gaseous HI, previously generated as described in the Exp. Sect., over the support. These conditions afforded the iodide derivative in nearly quantitative yield. This can be recovered and purified by elution with dichloromethane or another solvent through a small, commercially available Sep Pak alumina column.

The use of HBr instead of HI allows considerable reduction of the reaction time, as the bromination is complete in less than 20 s. Nevertheless, the silica purification process previously developed for the iodo derivative was inefficient and the best results were obtained with a homemade K_2CO_3 column.

Since the total recovery volume does not exceed 1.8−2.5 mL, an additional evaporation step is not required before alkylation. The [^{18}F]fluorobenzyl bromide derivative was obtained from no-carrier-added [^{18}F]fluoride in 35−40% radiochemical yields [EOB (end of bombardment)] with a radiochemical purity of > 98% within 40 min.

The following alkylation reaction, using phase-transfer techniques, is especially noteworthy because of its simplicity in contrast to other procedures that require anhydrous conditions for the deprotonation of a chiral auxiliary.

In practice, the [^{18}F]fluoro-arylated product (**3**) of 6-[^{18}F]fluoro-L-dopa was synthesized in a two-phase mixture containing *N*-(diphenylmethylene)glycine *tert*-butyl ester (**5**), *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium (**4**), [^{18}F]benzyl bromide **2**, cesium hydroxide and dichloromethane or toluene. Initial enantioselective catalytic phase-transfer alkylation was conducted by Corey's group in dichloromethane with 1 equiv. of the Schiff base, 0.1 equiv. of catalyst, 10 equiv. of cesium hydroxide and a large excess of alkylating agent (1.5−5 equiv.). Under these conditions, the reaction is described to proceed with high enantioselectivity (> 95%) with various benzyl halides at −78 °C for 24 h.[9]

Extrapolation of these reaction conditions to radiochemistry is not feasible. Indeed, a radiochemical synthesis starting from 100 mCi of [^{18}F]fluorobenzyl bromide of high specific activity (10 Ci/μmol) contains only a few micrograms of reagent (2.48 μg). Therefore, in order to obtain the best enantioselectivity and radiochemical yield, different reaction parameters (base, PTC and imine amounts, solvent and reaction temperature), keeping constant solvent volume (2 mL) and reaction time (10 min), were investigated. In all cases, the (*S*) absolute configuration and the enantiomeric excess (*ee*) were established after conversion of the [^{18}F]fluorinated alkylated product to the corresponding [^{18}F]fluorodopa. After preparative HPLC purification, the samples were analyzed on an analytical chiral column according to the method exemplified in the Exp. Sect. Although levels of induction are not affected by stirring rate, effective stirring is crucial in order to obtain rapid reaction.[16]

As can be seen from the results (Table 1), increasing the concentration of catalyst (**4**) has a positive result on the *ee* (Entries 1 and 2). In both cases, a high conversion (> 90%) of the [^{18}F]fluorobenzyl bromide into the corresponding alkylated product was also observed. From Entries 2−8, it appears that the *ee* tends to be lower when the concentration of the Schiff base increases, although in this instance the enantioselectivity of Entry 8 is somewhat higher than for Entry 7. The use of imine in a range of 1−5 mg affords similar enantioselectivities (Entries 3−6).

Table 1. Enantioselectivity of the reaction with reaction conditions; *n* = number of runs

Entry	CsOH mg (μmol)	**5** mg (μmol)	**4** mg (μmol)	Solvent	*T* [°C]	*ee* [%]	*n*
1	38 (226)	10 (32.8)	2 (3.1)	CH_2Cl_2	20	81	3
2	42 (250)	10.2 (34.5)	14.3 (22.4)	CH_2Cl_2	20	88	3
3	39 (232)	0.7 (2.4)	16 (25.1)	CH_2Cl_2	20	92	1
4	40 (238)	1.2 (4.1)	17.5 (27.4)	CH_2Cl_2	20	92	1
5	39 (232)	1.9 (6.4)	15.5 (24.3)	CH_2Cl_2	20	92	3
6	39 (232)	5 (16.9)	15.4 (25.4)	CH_2Cl_2	20	92	3
7	39 (232)	26.4 (89.4)	14.6 (22.9)	CH_2Cl_2	20	53	1
8	42 (250)	34 (115)	16.1 (25.2)	CH_2Cl_2	20	57	1
9	40 (238)	1.5 (5.1)	15.3 (24.0)	CH_2Cl_2	0	95	5
10	40 (238)	1.6 (5.4)	14.7 (23.0)	CH_2Cl_2	−20	95	2
11	39 (232)	1.8 (6.1)	15.5 (24.3)	CH_2Cl_2	−40	−	1
12	41 (244)	1.9 (6.4)	16.1 (26.6)	CH_2Cl_2	−78	−	1
13	41 (245)	1.5 (5.1)	16.3 (25.5)	toluene	0	96	> 10

In a last set of experiments, the temperature effect on the alkylation enantioselectivity was probed (Entries 9−12). Alkylations with the nca electrophilic agent were conducted at five different temperatures: −78 °C, −40 °C, −20 °C, 0 °C and ambient temperature. From these data, it appears that reaction temperature has only a slight effect on the asymmetric induction. A decrease of the temperature from room temperature to 0 °C and −20 °C increased the *ee* from 92 to about 95%. Substitution of CH_2Cl_2 by toluene also led to a light increase of the *ee* (Entry 13). However, at lower temperatures (−40 and −78 °C), the radiochemical yield decreased drastically, resulting in no alkylation reaction even after 1 h (Entries 11 and 12).

A reaction carried out using 50% aqueous potassium hydroxide as base shows that the alkylation reaction can be performed in the presence of large amounts of water (see Exp. Sect.). However, this last approach was not optimized (*ee* 86%).

Taking into account all these results, a higher enantioselectivity was obtained when the reaction proceeded at 0 °C in toluene in the presence of 1 equiv. of Schiff base (**5**; 6.8 μmol, 2 mg), 35 equiv. of cesium hydroxide (40 mg, 238 μmol) and 4.2 equiv. of catalyst (**4**; 15 mg, 24.8 μmol). In this case, we have to keep in mind that the above process cannot be called a catalytic process. The [^{18}F]electrophilic agent (10 nmol, 2.48 μg) is present, but in a very small amount compared to both the Schiff base (1.5×10^{-3} equiv.) and the quaternary ammonium salt (4×10^{-4} equiv.). However, this is not a problem since the reaction is run on a small scale, and the chiral reagent, which is now commercially available, is easily prepared in two steps from inexpensive cinchonidine.[9] The other major improvement, compared to the initial procedure using chiral auxiliaries,[5] is the high enantioselectivity observed at 0 °C and even at room temperature. Under the best conditions, more than 97% of the L form of 6-[^{18}F]fluoro-L-dopa is available at the end of the synthesis. Furthermore, this alkylation reaction is fast and complete even after 5 min. This nca synthesis of 6-[^{18}F]fluoro-L-dopa is a good illustration of the main differences that can exist between conventional and radiochemical chemistry.

Conclusion

In summary, a systematic study of PTC reaction conditions using various amounts of substrate, catalyst, solvent at different temperatures has led to a simple, stereoselective synthesis of 6-[^{18}F]fluoro-L-dopa. After preparative HPLC purification, the main radiochemical impurity was the D isomer of 6-[^{18}F]fluorodopa. When the alkylation reaction was conducted in toluene at 0 °C, only 2.0−2.5% of this isomer was detected. Although this simple method affords a lower enantiomeric excess (96%) than other published nca procedures, this general nca [^{18}F]fluorination route is well adapted for automation and future routine production of nca 6-[^{18}F]fluoro-L-dopa. Moreover, with further development of the phase-transfer catalysts, it should be possible in the future to optimize the efficiency of the alkylation step. Research continues towards extending this process to the preparation of other amino acids such as 2-fluoro-L-tyrosine and to simplify the preparation of the alkylating agent.

Experimental Section

Starting Materials: The aminopolyether "Kryptofix 222" (4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosan, K/

222), potassium carbonate, cesium hydroxide monohydrate, and hydroiodic acid were obtained from Merck. Sodium borohydride was purchased from Acros. ^{t}C18, Al_2O_3, SiO_2, QMA Sep Pak cartridges were obtained from Waters (Milford, MA, USA). The prochiral reagent *tert*-butyl glycinate, benzophenone imine and gaseous hydrobromic acid were purchased from Sigma−Aldrich. 6-[^{19}F]Fluoro-D,L-dopa was purchased from RBI (USA). Solvents were of HPLC grade from Baker and were filtered before use and, unless described, used without further purification. The trifluoromethanesulfonate salt of 2-dimethylaminoveratraldehyde (**1**) and the *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide catalyst (**4**) were synthesized according to literature procedures[5,9] and characterized by standard methods. ^{18}O-enriched water (95%) was obtained from Rotem Industry (Israel).

General: IR spectra were obtained with a Mattson Genesis series FTIR spectrometer. Melting points were recorded with a Büchi melting point apparatus and are corrected. NMR spectroscopy was carried out with a Bruker 400 NMR spectrometer (400 MHz) using $CDCl_3$ as a solvent unless noted and tetramethylsilane (TMS) as internal standard. The chemical shifts are reported in parts per million (ppm) from TMS. MS were recorded with an Automass solo from ThermoFinnigan (EI: 70 eV) or with LC MSMS using a "Triple-Stage quadrupole TSQ 7000" from Finnigan with electrospray source (ESI, HV 4.5 KV). Column chromatography was performed on 230 mesh silica gel from Merck. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 F254 silica plates and analyzed on a Berthold TLC scanner. TLC elution conditions varied and are specified individually for each compound. Radioactivity was measured in a dose calibrator and all radiochemical yields are decay-corrected unless noted. The synthesis was performed with a Zymate Laboratory Robot (Zymark Corp), which was described previously elsewhere.[17]

High-Performance Liquid Chromatography (HPLC) Separations. System A: Analytical HPLC was performed with a Waters 600E pump, a manual Rheodyne injector (200 μL loop), a Waters PDA and the Millennium® Chromatography Manager software from Waters. The analytical reverse phase Waters Symmetry® C18 column (150 × 3.9 mm, 5 μm particle size), protected with a Waters Sentry✓ guard column, was connected in series to an NaI detector for radioactivity detection. The elution was performed at a constant flow rate of 1 mL/min with a mixture consisting of CH_3CN/18 Megohms water. **System B:** The preparative HPLC of 6-[^{18}F]fluoro-L-dopa was conducted on an Econosphere C8 column (250.0 × 9 mm, 10 μm particle size Altech) with a Waters 600 pump, a manual Rheodyne injector (5000 μL loop), a Waters Lambda Max Model 481 UV spectrophotometer (281 nm). The mobile phase was aqueous acetic acid (0.1%) with ascorbic acid (0.01%) and EDTA (1 mM) and the flow rate was 5 mL/min. The radioactive elution profile was monitored with a homemade GM radioactivity detector.

Enantiomeric Excess Determination: The enantiomeric purity of the radiopharmaceutical was determined after HPLC purification under two different conditions. In both cases, similar enantiomeric excesses were obtained. **System C:** A chiral Pro=Si 100 column (Serva, Polylab, Antwerp, Belgium; 4.6 × 250 mm) was eluted at a flow rate of 1.5 mL/min with a mixture consisting of 50 mM KH_2PO_4 and 1 m M $CuSO_4$ at pH = 4. Under these conditions, the retention time of the D and L enantiomers was 6 and 9 min, respectively. **System D:** A CrownPak CR (+) column (4.0 mm I.D × 150 mm, 5 μm) from Daicel Chemical Industries (Tokyo, Japan) was eluted with aqueous $HClO_4$ (pH = 2.0) at a flow rate of 0.8 mL/min. The retention time of the D and L enantiomers was 8 and 11.2 min, respectively.

Nca [^{18}F]F$^-$ Production: Nca [^{18}F]fluoride was produced by proton irradiation (18 MeV, 30 μA, 20 min) of 95% enriched ^{18}O water in a silver target (2.2 mL internal volume) using an IBA compact cyclotron (Louvain La Neuve, Belgium) The target contents were delivered through 75 m of small-bore Teflon tubing (1.6 mm o.d. × 0.8 mm id) to the chemistry laboratory. The separation of nca [^{18}F]fluoride from ^{18}O-enriched water was realized on a small QMA Sep Pak light cartridge previously conditioned with 10 mL of 0.5 M K_2CO_3 and water (20 mL). Enriched water was recovered and after distillation used again for further production. The [^{18}F]F$^-$ trapped on the column was eluted into a round-bottomed open vial (2.5 mL, Wheaton) with 400 μL of a solution previously prepared by mixing of an equal volume of potassium carbonate in water (35 mg/mL) and kryptand in acetonitrile (110 mg/mL).

The [^{18}F]Fluorinating Agent: The water was evaporated under a stream of nitrogen for 5 min on an aluminum heating block at 120 °C. Acetonitrile was then added (100 μL) and the solution concentrated to dryness. The azeotropic evaporation step was repeated twice (2 × 100 μL) and finally a dry fluorinating agent in the form of a [^{18}F]potassium Kryptofix complex ([K/222]/^{18}F$^-$) was obtained.

Preparation of the Nca 2-[^{18}F]Fluoro-4,5-dimethoxybenzaldehyde: A solution of 15 mg of the trifluoromethanesulfonate salt of dimethylaminoveratraldehyde in 0.9 mL of DMSO was added to the previous residue of [K/222]/^{18}F$^-$. The vial was then closed with a screw cap and heated at 90 °C for 5 min. After labeling, the DMSO solution was diluted with water (30 mL) and the whole solution passed through a previously activated environmental ^{t}C18 Sep Pak cartridge. The radiochemical yield of the nca [^{18}F]fluoroveratraldehyde intermediate depends mainly of the quality of the starting triflate precursor and averaged between 40 and 50% EOB [R_f (CH_2Cl_2) = 0.46; t_R (HPLC) = 2.9 min (System A, CH_3CN/water, 80:20)].

Preparation of the Nca 2-[^{18}F]Fluoro-4,5-dimethoxybenzyl Alcohol: For the on-column reduction of the aldehyde to the alcohol, a solution of $NaBH_4$ in water (0.5 g/10 mL) was slowly passed through the ^{t}C18 cartridge (1 min). For subsequent quality controls, the 2-[^{18}F]fluoro-4,5-dimethoxybenzyl alcohol was eluted from the C18 cartridge with 2 mL of CH_3CN. TLC and HPLC analyses indicated that this reduction step was quantitative (95−100%). As an alternative to this procedure, reduction was conducted directly in the DMSO phase. In this case, after labeling, the DMSO solution was diluted with 20 mL of sodium borohydride solution (1 g/10 mL) and the whole solution passed through a previously activated environmental ^{t}C18 Sep Pak cartridge (Waters). This process proceeded also with quantitative yield [R_f (CH_2Cl_2) = 0.10; t_R (HPLC) = 2.5 min (System A, CH_3CN/water, 80:20)].

Preparation of the Nca 2-[^{18}F]Fluoro-4,5-dimethoxybenzyl Bromide Alkylating Agent (2, X = Br): After reduction, the Sep Pak column was washed with 10 mL of highly pure water. The residual water on the cartridge was then displaced with hexane (3−5 mL). Hexane (500 μL) was kept in the buffer volume above the ^{t}C18 cartridge. Halogenation was then performed directly on the cartridge with gaseous hydrogen bromide during 20 s. An exothermic reaction took place on the support and hexane was then removed. After reaction, the Sep Pak cartridge was flushed with nitrogen for 2 min and the corresponding [^{18}F]fluorobenzyl bromide derivative eluted with dichloromethane or toluene (3.5 mL). The residual unchanged HBr was removed by passing the solution through a small potas-

sium carbonate column (5 mm i.d. × 30 mm) [R_f (CH_2Cl_2) = 0.6; t_R (HPLC) = 3.2 min (System A, CH_3CN/water, 80:20)].

Preparation of the Nca 2-[^{18}F]Fluoro-4,5-dimethoxybenzyl Iodide Alkylating Agent (2, X = I): Halogenation was also performed on the cartridge with gaseous hydrogen iodide generated by heating liquid HI at 150 °C under a flow of nitrogen. In this case the reaction was slower (10 min). After iodination, the support was flushed with nitrogen for 2 min and the corresponding [^{18}F]fluorobenzyl iodide derivative eluted with dichloromethane or toluene (4 mL). The residual unchanged HI and other impurities were removed by passing the mixture through an SiO_2 Sep Pak column. The yield and radiochemical purity of the product were determined by radio TLC and HPLC analyses [R_f (CH_2Cl_2) = 0.6; t_R (HPLC) = 3.2 min (System A, CH_3CN/water, 80:20)].

General Reaction Procedure for the [^{18}F]Alkylation of the Schiff Base 5. Method I: Alkylation was performed under agitation in a conical flask (10 mL, Wheaton) containing 2 mg (6.8 μmol) of the Schiff base **5**, 15 mg (24.8 μmol) of the *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide catalyst (**4**) and 40 mg (238 μmol) of cesium hydroxide monohydrate as base. To this vial, cooled to 0 °C, was added the nca fluorobenzyl halide **2** in toluene (2 mL). The alkylation reaction was performed at this temperature for 10 min and the organic mixture quenched at 0 °C with 250 μL of HI (57% w/v) previously distilled from red phosphorus. In order to evaluate the yield of the alkylation step, an aliquot was assayed before HI addition and directly analyzed both by TLC and HPLC [R_f (CH_2Cl_2) = 0.17; t_R (HPLC) = 6.5 min (System A, CH_3CN/water, 80:20)]. The experiments were also conducted at different temperatures with various amounts of base, imine and catalyst (see Results and Discussion section). **Method II:** A liquid/liquid PTC was also realized with 50% aqueous potassium hydroxide as base. In this case, 1 mL of this solution was mixed with 1 mL of toluene containing 2 mg (6.8 μmol) of the prochiral Schiff base, 10 mg (16.5 μmol) of the *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide catalyst and the nca **2**. The reaction was conducted at 0 °C or room temperature for 10 min [RY (radiochemical yield): 85%].

6-[^{18}F]Fluoro-L-dopa: Toluene was evaporated at 130 °C and additional HI added (750 μL). The vial was closed and the solution refluxed (200 °C) for 15 min. Following hydrolysis, the solution was cooled and diluted with 1.5 mL of HPLC eluent. The 6-[^{18}F]fluoro-L-dopa was finally purified by preparative HPLC (Condition B). Under these conditions 6-[^{18}F]FDOPA was eluted between 8 and 9 min.

2-[^{19}F]Fluoro-4,5-dimethoxybenzyl Alcohol: A solution of $NaBH_4$ (2 g, 52.9 mmol) in water (20 mL) was slowly added to a suspension of 6-fluoroveratraldehyde (5 g, 27.2 mmol) in ethanol (200 mL). The reaction mixture was stirred at room temperature for 15 min and then diluted with water (500 mL). The water/ethanol mixture was extracted twice with EtOAc. The extracts were dried with $MgSO_4$, filtered and the solvents evaporated to dryness. Crystallization from diethyl ether afforded the benzylic alcohol as white crystals (4.8 g, 95%). M.p. 55−56 °C. IR (KBr): $\tilde{\nu}$ = 3292, 1625, 1519, 1234, 1196, 1107 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H, OC*H*$_3$), 3.85 (s, 3 H, OC*H*$_3$), 4.49 (s, 2 H, C*H*$_2$OH), 6.59 (d, $^3J_{H,F}$ = 10.96 Hz, 1 H, Ar*H*), 6.79 (d, $^4J_{H,F}$ = 7.3 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 57.1 (OCH_3), 57.3 (OCH_3), 59.8 (CH_2), 100.9 (d, $^2J_{C,F}$ = 27.5 Hz Ar−C), 112.6 (d, $^3J_{C,F}$ = 4.9 Hz, Ar-C), 119.2 (d, $^2J_{C,F}$ = 16.2 Hz, Ar-C), 146.3 (Ar-C), 150.3 (d, $^3J_{C,F}$ = 9.7 Hz, Ar-C), 156.7 (d, $J_{C,F}$ = 237.8 Hz, Ar−F) ppm.

2-[^{19}F]Fluoro-4,5-dimethoxybenzyl Bromide (2): A solution of 2-[^{19}F]fluoro-4,5-dimethoxybenzyl alcohol (2 g, 10.7 mmol) in diethyl ether (dry, 70 mL) saturated with HBr(g) was stirred at room temperature for 30 min. At this time, as indicated by HPLC, the reaction was quantitative. The reaction mixture was then treated with a saturated $NaHCO_3$ solution. The ether phase was recovered and dried with $MgSO_4$. The solvent was then removed under reduced pressure to give **2** (2.4 g, 90%) as a white solid which decomposes slowly. M.p. 59−61 °C. IR (KBr): $\tilde{\nu}$ = 2925, 2854, 1515, 1131, 1108 cm^{-1}. ^{1}H NMR(400 MHz, $CDCl_3$): δ = 3.85 (s, 3 H, OC*H*$_3$), 3.86 (s, 3 H, OC*H*$_3$), 4.51 (s, 2 H, C*H*$_2$OH), 6.61 (d, $^3J_{H,F}$ = 10.92 Hz, 1 H, Ar*H*), 6.81 (d, $^4J_{H,F}$ = 7.0 Hz, 1 H, Ar*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.5 (CH_2Br), 56.2 (OCH_3), 56.4 (OCH_3), 100.1 (d, $^2J_{C,F}$ = 27.5 Hz, Ar-C), 112.7 (d, $^3J_{C,F}$ = 4.85 Hz, Ar-C), 115.4 (d, $^2J_{C,F}$ = 16.2 Hz, Ar-C), 145.4 (Ar-C), 145.4 (Ar-C), 150.4 (Ar-C), 154.9 (d, $J_{C,F}$ = 241 Hz, Ar−F) ppm. EI-MS: *m*/*z* (%) = 248 (18) [M^+, ^{79}Br], 169 (100) [$M - {}^{79}Br]^+$.

Synthesis of the Alkylated Schiff Base 3: A solution of 2-fluoro-4,5-dimethoxybenzyl bromide (**2**; 624 mg, 3.4 mmol) in CH_2Cl_2 (2 mL) was added to a mixture of *tert*-butyl *N*-(diphenylmethylene)glycinate (**5**; 1.0 g, 3.4 mmol), $CsOH·H_2O$ (2.8 g, 17 mmol), and the catalyst $Bu_4N^+Br^-$ (11 mg, 0.034 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was then stirred vigorously at room temperature. After 30 min, the alkylation was quantitative as demonstrated by analytical HPLC (System A). Water was added (20 mL), the two phases were separated and the water solution extracted twice with diethyl ether (2 × 10 mL). The combined ether phases were dried with magnesium sulfate, then concentrated under reduced pressure to give the crude product **3** as a yellow oil (1.34 g, 2.89 mmol, 85%). Purification of the crude product by column chromatography on silica gel afforded the alkylation product **3** (hexanes/CH_2Cl_2/ET_3N, 70:30:3) as a yellow oil (1.1 g, 70%). TLC: R_f (silica gel) = 0.38 (hexanes/CH_2Cl_2/Et_3N, 70:30:3). IR (neat, NaCl): $\tilde{\nu}$ = 2963, 2932, 2870, 1732, 1514, 1447, 1286, 1227, 1191, 1152, 700 cm^{-1}. ^{1}H NMR(400 MHz, $CDCl_3$): δ = 1.43 [s, 9 H, C(CH_3)$_3$], 3.09 (dd, *J* = 9.6, 13.2 Hz, 1 H, H-3′), 3.22 (dd, *J* = 3.6, 13.6 Hz, 1 H, H-3), 3.6 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 4.14 (dd, *J* = 4.0, 9.3 Hz, 1 H, H-2), 6.49 (d, *J* = 7 Hz, 1 H, ArH), 6.58 (br. d, *J* = 10.9 Hz, 1 H, ArH),), 6.67 (d, *J* = 6.6 Hz, 2 H, ArH), 7.37−7.24 (m, 6 H, ArH), 7.57 (d, *J* = 7.3 Hz, 2 H, Ar*H*) ppm. ^{13}C NMR ($CDCl_3$/100 MHz): δ = 27.9 [C(*C*H$_3$)$_3$], 31.8 (CH_2), 55.50 (OCH_3), 55.53 (OCH_3), 66.0 (CH), 80.5 [*C*(CH$_3$)$_3$], 99.2 (d,$^2J_{C,F}$ = 27.5 Hz, Ar-C), 113.8 (d,$^3J_{C,F}$ = 4.85 Hz, Ar-C), 115.1(d,$^2J_{C,F}$ = 17.8 Hz, Ar-C), 126.6, 127.4, 127.6, 128.2, 129.7, 135.7, 139.0, 144.2 (10 Ar-C), 147.8 ($^3J_{C,F}$ = 9.7 Hz, Ar-C), 154.8 (d, $^1J_{C,F}$ = 237.8 Hz, Ar-C), 169.8 (C=N), 170.0 (CO) ppm. ES-MS (ESI): *m*/*z* = 464.3 [M + H]$^+$.

Acknowledgments

This work, the preliminary results of which were previously presented as an oral communication at the Thirteenth International Symposium on Radiopharmaceutical Chemistry, St Louis, USA, June 27−July 1, 1999, was supported by the "Fonds National de la Recherche Scientifique" (grants 3.4526.96 and 3.4513.01), the Fonds spéciaux ULG and the INSERM/CFB exchange. A. P. is a research associate of FNRS Belgium.

[1] E. S. Garnett, G. Firnau, C. Nahmias, *Nature* **1983**, *305*, 137−138.
[2] M. E. Phelps, *Annu. Rev. Nucl. Part. Sci.* **2002**, *52*, 303−338.
[3] A. Luxen, M. Guillaume, W. P. Melega, V. W. Pike, O. Solin, R. Wagner, *Nucl. Med. Biol.* **1992**, *19*, 149−158.
[4] E. F. de Vries, G. Luurtsema, M. Brüssermann, P. H. Elsinga, W. Vaalburg, *Appl. Radiat. Isot.* **1999**, *51*, 389−394.

[5] C. Lemaire, P. Damhaut, A. Plenevaux, D. Comar, *J. Nucl. Med.* **1994**, *35*, 1996−2002.
[6] D. Seebach, E. Dziadulewicz, L. Behrendt, S. Cantoreggi, R. Fitzi, *Liebigs Ann. Chem.* **1989**, *12*, 1215−1232.
[7] K. Maruoka, T. Ooi, *Chem. Rev.* **2003**, *103*, 3013−3028.
[8] M. J. O′Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353−2355.
[9] E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415.
[10] E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347−5350.
[11] B. Lygo, P. G. Wainnwright, *Tetrahedron Lett.* **1997**, *38*, 8595−8598.
[12] C. Lemaire, P. Damhaut, A. Plenevaux, R. Cantineau, L. Christiaens, M. Guillaume, *Appl. Radiat. Isot.* **1992**, *43*, 485−494.
[13] R. Iwata, C. Pascali, A. Bogni, G. Horvath, Z. Kovaacs, K. Yanai, T. Ido, *Appl. Radiat. Isot.* **2000**, *52*, 87−92.
[14] S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Leach, D. A. Longbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815−4195.
[15] C. Lemaire, P. Damhaut, B. Lauricella, C. Mosdzianowski, J.-L. Morelle, M. Monclus, J. Van Naemen, E. Mulleneers, J. Aerts, A. Plenevaux, C. Brihaye, A. Luxen, *J. Labelled Compd. Rad.* **2002**, *45*, 435−447.
[16] M. J. O'Donnell, F. Delgado, C. Hostettler, R. Schwesinger, *Tetrahedron Lett.* **1998**, *39*, 8775−8778.
[17] C. Brihaye, C. Lemaire, Ph. Damhaut, A. Plenevaux, D. Comar, *J. Labelled Compd. Rad.* **1994**, *35*, 160−162.

Received January 30, 2004

